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Review Article

Myelodysplastic Syndrome Can Lead to Acute Myeloid Leukemia

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ABSTRACT

Myelodysplastic syndrome causes ineffective haematopoiesis which is indicated by bone marrow failure. In some patients MDS may transform to acute myeloid leukemia (AML). The inherited sites on the genome (genetic loci) that contribute to myelodysplastic syndrome (MDS) development are being identified in a growing number in both children as well as adults. Various environmental and iatrogenic etiologies have been implicated in MDS, including exposure to chemotherapy, radiation or environmental toxins such as benzene. MDS may be clinically asymptomatic for years and may have incidental findings of cytopenias on routine labs. Some patients may present with signs and symptoms related to bone marrow failure such as fatigue, bleeding, or infections. Clinical manifestations may include a decrease in the number of red blood cells, platelets, and white blood cells. As some patients develop acute leukemia, MDS has also been referred to as preleukemia or a preleukemic condition.

Keywords: Myelodysplastic Syndrome, acute myeloid leukemia, red blood cells, platelets, and white blood cells.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic neoplasms classically described as a clonal disorder of hematopoietic stem cells leading to dysplasia and ineffective hematopoiesis in the bone marrow. Some patients with MDS may have a transformation into acute myeloid leukemia (AML). MDS is usually diagnosed in older patients over the age of 65. Clinical manifestations include a decrease in the number of red blood cells (RBC), platelets, and white blood cells (WBC). The disease course is variable. Not all patients require treatment initially, as there is no survival benefit with the treatment of asymptomatic, low-risk patients. Treatment is reserved for symptomatic patients, such as those requiring frequent blood transfusions. Prognosis and overall survival depend upon multiple factors such as the severity of cytopenias, the percentage of blasts in the peripheral blood and bone marrow, and karyotype.

Etiology

MDS is a clonal disorder of myeloid stem cells which may occur de novo or secondary to various insults to the bone marrow. Various environmental and iatrogenic etiologies have been implicated in MDS, including exposure to chemotherapy (alkylating agents in particular), radiation or environmental toxins such as benzene. Familial MDS has been reported but is a rare entity[1]. The actual preceding factor(s) for de novo MDS is not entirely understood but assumed to occur from an oncogenic process resulting in one or more somatic mutations. Over recent years, we have gained much insight into mutations that are commonly altered in MDS due to advances and rapid availability of gene sequencing. With these developments, researchers can identify one or more driver mutations in up to 80% to 90% of patients with some of the most common ones including *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53*, and *EZH2. RUNX1,* for example, is a mutation noted to disrupt normal hematopoiesis. More than 100 genes have been found to be recurrently mutated in MDS, and these encode spliceosome components, chromatin remodeling factor[2].

These driver mutations have been found to correlate with different clinical features, including the severity of cytopenias, blast percentage, cytogenetics, and overall survival. Of note, genetic mutations are not included in prognostic scoring systems for MDS but they have been found to influence overall survival in some cases. TP53 for example, is a tumor suppressor gene that has a poor prognosis compared to other mutations [3]. MDS may be de novo or related to prior use of chemotherapeutic agents, also known as treatment-related MDS (t-MDS). This entity is associated with a poor prognosis compared to de novo MDS and typically occurs five to seven years after use of chemotherapeutic agents [4].

Alkylating agents such as cyclophosphamide have been associated with this type of MDS. t-MDS is commonly associated with monosomies in chromosome 5 or 7 and complex cytogenetics. This type of MDS also commonly transforms into acute myeloid leukemia (AML.) In a retrospective review of 112 patients with t-MDS, 55% transformed into acute myeloid leukemia, while de novo MDS transforms into AML only around 30% of the time. The median overall survival for secondary, or treatment-related MDS, is only around 30 weeks [5].

Epidemiology

The incidence of de novo MDS in the United States varies but Surveillance Epidemiology and End Results (SEER)-Medicare database from 2007 through 2011 estimate

incidences around 4.9 per 100,000 persons and around 20,541 new cases annually. The incidence of MDS increases with age with most cases occurring after age 65 and most frequently seen in patients over 80 years old, with a rate of 58 per 100,000. It is usually seen more in males and Caucasians[6].

Pathophysiology and etiology

The early stages of MDS, excessive programmed cell death (apoptosis) is the predominant event with subsequent cytopenia with its variable degree and extent. Furthermore, with disease progression, gene mutation, and leukemic transformation, causing smashing of BM via the leukemic cells. Clonal mutation is the trigger for MDS development leading to normal stem cell suppression. This mutation may result from genetic susceptibility or damage of hematopoietic stem cells.

Most patients with MDS have no apparent cause (approximately 80%) and named as idiopathic or primary. Secondary MDS according to The World Health Organization (WHO) develops years after exposure to known agents causing chromosomal damage such as chemotherapy (alkylating agents, topoisomerase II inhibitors), radiotherapy, heavy metals (mercury, lead), viral infection, toxic chemicals (benzene, fungicide), and some autoimmune conditions. Chemotherapy-related MDS represented the most obvious causal factor. We have 2 types of therapy; alkylating agents ± adiotherapy and topoisomerase II inhibitors. The developed MDS had special featured depending on the offending risk factor. Post alkylating agents such as Nitrogen mustards, characterized by late onset about 5-7 years after exposure with specific karyotyping (-5, del(5q), -7, del(q) and complex). While in case of post topoisomerase II inhibitors such as anthracycline /etoposide, characterized by early onset 1-3 years with chromosomal. Although genetic predisposition is rare, familial incidences are reported. Familial platelet disorder is the best example characterized by a mutation in RUNX1 and GATA2 predisposing to MDS. Familial AML with mutated CEBPA and telomere biology disorders are another forms of familial MDS may be detected during family members screening for BM transplantation. Two-hit model of progression from chronic MDS into AML may help in understanding the basic of leukemic transformation. It may include molecular and cytogenetic aberrations either in first or second hit class mutations during the disease progression. Actually, the mechanisms of leukemic transformation are not clearly understood.

Signs and symptoms of MDS

Clinical manifestations of MDS are non-specific and vary considerably depending on subtype and severity of cytopenias. A diagnostic workup for MDS is often, but not always, triggered by symptoms or signs suggestive of cytopenias, including fatigue and decline in living activities indicative of anemia, infections indicative of neutropenia, and frequent or unexplained bleeding and bruising indicative of thrombocytopenia[9, 10].

Classifications[11]

Subtype	Blood	Bone marrow
MDS-SLD	Single or bi-cytopenia	Dysplasia ≥10% of on cell line, <5% blasts
MDS-RS	Anemia, no blasts	≥15% of erythroid precursors with RS or ≥5% RS if SF3B1 mutation is present.
MDS-MLD	Cytopenias <1×109/L monocytes	Dysplasia ≥10% of cells in ≥2 hematopoietic lineages, <15% RS or <5% RS if SF3B1 mutation present) <5% blasts
MDS-EB-1	Cytopenias ≤2%-4% blasts, <1 ×109/L monocytes	SLD or MLD, 5%-9% blasts, no auer Rods
MDS-EB-2	Cytopenias, ≤5%-19% blasts, <1 ×109/L monocytes	SLD or MLD, 10%-19% blasts, ± auer Rods
MDS-U	Cytopenias, ±1% blasts on at least 2 occcasions	SLD or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Uni-lineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q)
Refractory cytopenia of childhood	Cytopenias <2% blasts	Dysplasia 1-3 lineages, <5% blasts

MDS-SLD, MDS with single lineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-MLD, MDS with multilineage dysplasia; MDS-EB-1, MDS with excess blasts-1; MDS-EB-2, MDS with excess blasts-2; MDS-U, unclassifiable MDS. Lineage dysplasia includes Refractory anemia, Refractory neutropenia, and Refractory thrombocytopenia depending on number of cell lines involved (uni-lineage, bi-lineage or multi-lineage). Adapted from NCCN guidelines version 1 (2019).

Cytogenetic studies[12]

The cytogenetics role is gaining a great importance owing to the nonspecific histopathological changes. Some investigators claimed up to79% rate of chromosomal abnormalities in primary MDS. Patients with MDS fall into three categories: complex karyotypes (>3 abnormalities), normal karyotype, and balanced chromosomal abnormality. The chromosomal abnormalities may be multiple and indicate poor prognosis and may be single and usually indicates good prognosis except those with chromosome 7. The most common chromosomal abnormalities are monosomy 7 (-7) or 7q-, 5q-, trisomy 8 (+8). Presence of karyotype t (8:21), t (15,17), and inversion 16 denote AML rather than MDS.

Clinical Presentation

The MDS represent a heterogeneous group of clonal disorders in which the hematopoietic progenitor cells have a reduced ability to differentiate and are more likely to undergo apoptosis. This leads to bone marrow hyperplasia in most cases, as well as ineffective hematopoiesis that manifests with varying degrees of peripheral cytopenias [13].

Anemia (typically macrocytic) is the most common peripheral blood abnormality, occurring in approximately 80% to 85% of patients.4 Thrombocytopenia occurs in around 30% to 45% of MDS cases, with approximately 40% of patients found to have neutropenia at diagnosis [14].

Histopathology

Evaluation of the complete blood count (CBC) usually reveals anemia or pancytopenia. A bone marrow biopsy and aspirate are usually performed after exclusion of other causes of their cytopenias. There is no one histopathologic feature that defines MDS but rather a constellation of findings from the peripheral blood and bone marrow which meet the accepted criteria for diagnosis. Additional diagnostic workup includes flow cytometry immunophenotyping, cytogenetics with karyotype and fluorescent in situ hybridization (FISH), along with genetic profiling to assess for relevant somatic mutations[15].

Diagnosis

In most cases, those involved in diagnosing MDS are family doctors and hematologists. This is because it is often the family doctor who identifies anemia during a routine examination, or else MDS is identified on the basis of blood tests carried out to investigate the cause of symptoms of anemia. Once the more frequent causes of anemia have been ruled out, such as iron deficiency, vitamin B_{12} and folic acid deficiency, and hemolysis, referral to a hematologist for further investigation is advisable. In particular, the presence of bi- or pancytopenia (about 30%) can be a warning signal (red flag) and may indicate bone marrow disease. If blood cell counts and the differential cell count are normal, MDS is extremely unlikely. Patients who have undergone chemotherapy for any other disease, benign or malignant, especially with alkylating drugs (cyclophosphamide, ifosfamide, carmustine, dacarbazine, and others) and/or radiation therapy or radioiodine therapy in the past are at greater risk of developing MDS: around 10% of MDS patients developed the disease after treatment with cytotoxic agents or radiation[16].

Diagnosis is also confirmed by performing a bone marrow aspiration and biopsy. The bone marrow biopsy allows for determination of bone marrow cellularity and architecture. Diagnosis is established by the presence of dysplasia. A number of morphological classifications are in place to classify patients with MDS. The most recent one being the 2008 WHO version which was recently revised in 2016 [17].

In general, diagnosis is obvious in patients with excess blasts. The problem is in patients without excess blasts where diagnosis is based on dysplasia. Clinical assessment is needed in patients with minimal or not diagnostic evidence of dysplasia. In these cases, it is recommended that other causes of cytopenia be excluded. Routine tests include the analysis of anemia and thrombocytopenia, and exclusion of cause of blood loss or inflammatory processes. When suspected, evaluation of GI tract needs to be considered. Once other potential causes of cytopenia are excluded, additional diagnostic tools including cytogenetic evaluation, flow cytometry and, more recently, DNA sequencing, can help define the diagnosis and predict patient outcomes. Patients with cytopenia but no dysplasia are considered in the subset of idiopathic cytopenia of undetermined significance (ICUS). A fraction of these patients may have cytogenetic abnormalities and, up to 36% may carry 1 or more somatic mutations in genes recurrently mutated in myeloid malignancies [18].

Diagnose myelodysplastic syndromes [19]

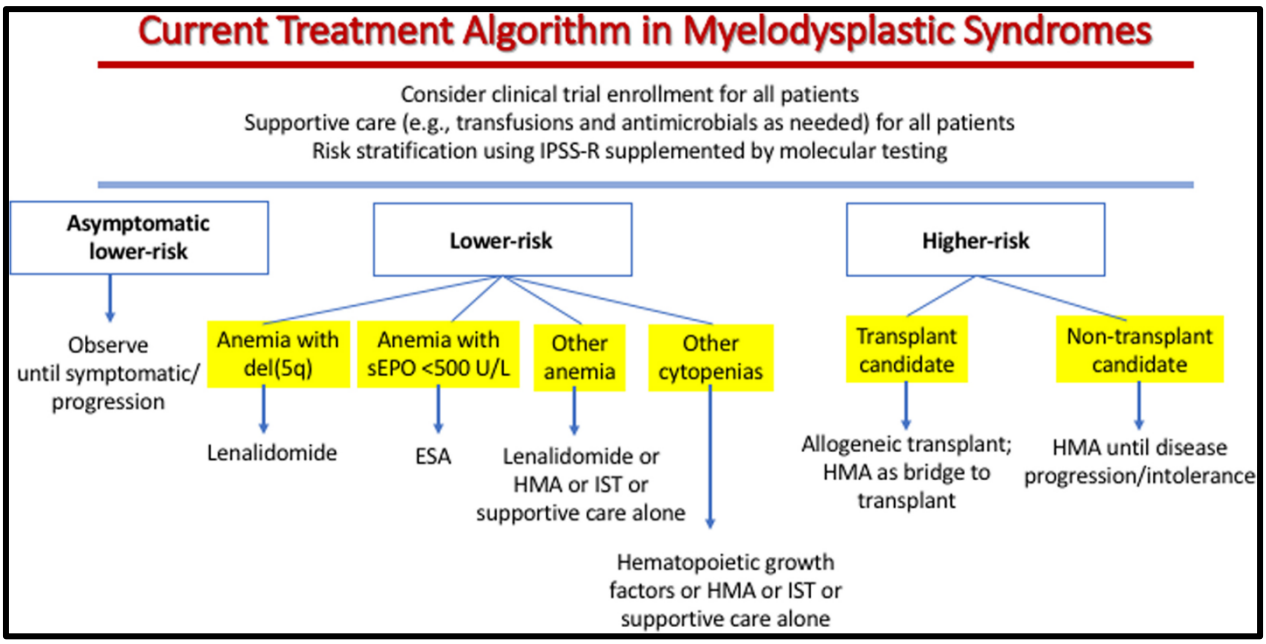
- **Peripheral blood**
  - **Blood count, mandatory**
    - ✓ Leukocyte count often <4000/µL
    - ✓ Platelet count often <100 000/µL
    - ✓ Hemoglobin often <12 g/dL
    - ✓ Reticulocyte count often low
  - **Differential blood count, manual, mandatory**
  - **LDH U/L** -(above the norm is associated with poorer prognosis)
  - **Ferritin**- If values >1000 µg/L, iron chelation therapy may be indicated
  - **Erythropoietin concentration**- If values <500 U/L, erythropoietin therapy may be indicated (off label)
  - **HLA typing in younger patients**- Allogenic transplantation may be indicated
  - **Bone marrow**
    - ✓ **Cytology** with myeloperoxidase stain, esterase stain, and staining for iron (dysplasia? percentage of blast cells?), mandatory

- ✓ **Cytogenetic testing**, may include FISH (chromosomal abnormalities?), mandatory
- ✓ **Histological analysis** of a bone marrow sample (cellularity? fibrosis?), mandatory
- ✓ **Immunophenotyping**, recommended

- **Peripheral blood or bone marrow.**

Treatment

A basic principle is that, for low-risk patients, the priority is maintenance or restoration of quality of life, whereas for high-risk patients, prolonging life expectancy is also an important therapeutic goal [20, 21]. Treatment should not be delayed until leukemia has developed, but should start as soon as the patient has complaints that impair his or her quality of life or has a high-risk profile. The mainstay of all treatments is transfusion of red blood cell concentrates and, for patients with bleeding and/or platelet counts in single figures, platelet concentrates. Typically, transfusions are given to patients with hemoglobin values below 8 to 9 g/dL .



Lower Risk MDS

Some patients with MDS have mild cytopenias and are asymptomatic at the time of diagnosis. Early treatment of MDS is not known to be beneficial in terms of preventing clonal evolution or death. Therefore, observation is appropriate for asymptomatic lower risk patients until their cytopenias worsen or they become more symptomatic [22].

For patients with lower risk disease and anemia associated with MDS, two parameters are important in treatment choice . First, the serum erythropoietin (sEPO) level reflects endogenous renal response to anemia and is a strong predictor of the likelihood of clinical response to ESA.

Hellstrom-Lindberg, E. et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Patients with lower risk MDS who have a sEPO < 100 U/L have a greater than 70% chance of responding to ESA, while for those patients with sEPO > 500 U/L, a trial of ESA is usually not warranted because the response rate is <10%. Second, the presence of a clonally restricted deletion of the long arm of chromosome 5 including band q31 (del5q) is associated with a high erythroid response rate to lenalidomide (65–70% transfusion independence, and 30–40% cytogenetic remission)[23].

Higher risk MDS

Allogenic blood stem cell transplantation is the only therapeutic measure that offers a potential cure to appropriate patients. Allogeneic hematopoietic cell transplantation in patients age 60-70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: comparison with patients lacking donors who received azacitidine 24.

This treatment is appropriate for patients aged up to 70 years without relevant comorbidities. In exceptional cases, patients aged over 70 have successfully undergone transplantation. The time point for transplantation is largely determined by the disease pathology. In patients with low and intermediate disease risk, transplantation should not be carried out until progression occurs. Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. final results of a prospective randomized european intergroup trial.

Post-transplantation aftercare is particularly important, so that complications and any incipient relapse may be

recognized at an early stage. The main complications are direct consequences of the conditioning, such as mucositis, bleeding, and infection during the time of cytopenia, and acute and chronic graft-versus-host disease, which can damage organs directly or indirectly, since the immune suppression required to treat it promotes severe bacterial and viral infections. At present, the therapy-related mortality rate is between 15% and 30%. Around 30% to 50% of patients can be cured by allogenic transplantation, and in 30% to 50% the MDS recurs [25, 26].

It is not clear whether treatment of higher risk MDS prior to ASCT is beneficial, but pre-transplant bridging therapy is often considered to cytoreduce disease, especially for those patients who are going to go on to get RIC approaches and those who have more than 10% marrow blasts. Pre-transplant cytoreductive therapy can also be considered in those for whom there will be a delay in transplant due to lack of donor availability or insurance approval. Pre transplantation therapy with azacitidine vs induction chemotherapy and post transplantation outcome in patients with MDS [27, 28].

For those patients who are not transplant candidates, HMA therapy is most appropriate. In a randomized trial of 358 higher risk MDS patients, azacitidine treatment was associated with a median survival of 24 months compared to 15 months in patients treated with intensive chemotherapy, low-dose cytarabine, or best supportive care.

Supportive care

Support of patients with severe symptomatic anemia with red cell transfusions and severe thrombocytopenia with platelet transfusions is a mainstay of therapy for MDS. Cause of death in patients with lower-risk myelodysplastic syndrome. Fevers in patients with MDS must be taken seriously, and antimicrobial protocols for febrile neutropenia followed carefully, as infection is the leading cause of death in MDS. The benefit of prophylactic antimicrobials is controversial [29]. For patients with thrombocytopenia who are refractory to platelet transfusions, the TPO agonists mentioned above may be of help, and the antifibrinolytic agents epsilon-aminocaproic acid or tranexamic acid can reduce bleeding in some of those with recurrent mucosal hemorrhage. Androgens such as danazol or oxymetholone may improve hemoglobin or platelet count in a minority of patients, but liver tests must be monitored during therapy and some older men may have difficulty with urinary retention due to an increase in prostate hyperplasia [30].

CONCLUSION

Myelodysplastic syndromes are conditions that can occur when the blood forming cells in the bone marrow become abnormal. This leads to low numbers of one or more types of blood cells. MDS is considered a type of cancer. Myelodysplastic syndrome (MDS) is primarily a disease of older adults. Symptoms mainly include anemia, leukopenia, and thrombocytopenia, but often found during routine laboratory investigations in asymptomatic patients. Diagnosed when bone marrow demonstrates significant dysplasia, clonal cytogenetic abnormality, quantitative changes in at least one of the blood cell lines, and blasts <20%.

Treatment is often based on supportive measures, including red cell and platelet transfusions. Chemotherapy agents such as azacitidine, lenalidomide, and decitabine are used for certain patients. Stem cell transplant is the only potentially curative therapy.

Many have a prolonged course with anemia and neutropenic infections, or may progress rapidly to acute myelogenous leukemia (AML). However, most patients die of infection while in the MDS stage of their disease.

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